REMARKS/ARGUMENTS

The enclosed remarks and submissions addresses the Examiner's objections as detailed in a Final Office Action dated September 22, 2004. Claims 7-10 and 23-28 remain in the present application.

Claims 7-10 and 23-28 have been rejected by the Examiner in the above-mentioned Final Office Action. Applicant submits that comments and evidence are herein provided to traverse the Examiner's opinion in this regard, while supporting the claims as they presently stand. Specifically, Applicant herein provides both third party expert opinion (Exhibit A) and factual evidence (Exhibit B) together with the comments made hereinbelow as support for the claims of the present application.

Claims 7-10 and 23-28 were previously rejected under 35 USC 112, 1st paragraph, for failure to comply with the written description requirement. Although Applicant's previous arguments have been deemed not persuasive, Applicant once again respectfully traverses the Examiner's objections in this regard. To this end, Applicant further submits that a person of skill in the art would understand the present application to teach the use of PEX modulation in a manner as presently claimed. Furthermore, Applicant herein provides a Declaration from Dr. Arthur E. Broadus (Exhibit A) which illustrates the understanding of the claimed invention, as taught in accordance with the present application by "a person of skill in the art". As detailed in the Curriculum Vitae included in Exhibit A, Dr. Broadus is an expert in the field of metabolic bone disease. Specifically, the Examiner is directed to the comments of Dr. Broadus, in paragraph 7 of the enclosed Declaration under 37 CFR 1.132 (Exhibit A) wherein he states that:

> "based on the findings of the above-captioned application, I would clearly understand that inhibition of PEX would be expected to result in 1) an increase in local endogenous PTHrP levels in or bound to osteoblasts and 2) would also be expected to prolong the "on time" of PTH bound to local osteoblastic PTH/PTHrP receptors and thereby potentiate PTH effects on these cells.

Furthermore, Dr. Broadus states, at paragraph 8 that:

> "I believe the above-noted application provides factual evidence and soundly predicts that PEX inhibitors, such as phosphoramidon, would result in an increase in PTH and/or PTHrP levels in the microenvironment of PTH/PTHrP receptors on osteoblasts, which would in turn lead to increase in bone formation. This approach represents a novel method of regulating bone formation that could form the basis of a novel therapy for osteopenic/osteoporotic states in humans."

Applicant thus maintains that the subject matter of the rejected claims is sufficiently described in the present application so as to provide a person of skill in the art with an understanding of the scope of the invention possessed by the Applicant at the time the application was filed. Applicant believes that the present application details the invention in a sufficient capacity so as to fairly predict the use of PEX modulation in the treatment of metabolic bone disease. Specifically, Dr. Broadus's comments further support the use of a compound to inhibit PEX activity so as to illicit a novel therapeutic effect, based on the teachings of the present application.

In view of the above, Applicant once again respectfully traverses the Examiner's rejections in this regard, and respectfully requests reconsideration thereof.

Considering the Examiner's objections with respect to enablement under 35 USC 112, first paragraph, Applicant submits that in addition to the comments and arguments countering the Examiner's rejections in this regard, as provided by way of this response, additional data is herein provided in Exhibit B. Applicant submits that Exhibit B provides further enabling evidence in support of the claims of the present application. Specifically, Applicant believes the teaching of the present application together with the data, as presented herein as Exhibit B would clearly enable a person of skill in the art to make and/or use the invention as claimed. The data presented in Exhibit B illustrates the modulation of PTHrP when *PEX* is inhibited by phosphoramidon, both *in vitro* and *in vivo*. These findings further corroborate with the teachings of the present application in that they support the therapeutic

effect of such modulation *in vivo* whereby an elevation in serum osteocalcin levels (a marker for bone formation) is evident.

As indicated in paragraphs 24 and 25 of the enclosed Declaration, the Examiner will note that Dr. Broadus believes that the therapeutic potential of the present invention is evidenced by the *in vivo* results as provided in Exhibit B.

Applicant wishes to point out that in view of the comments outlined in the enclosed Declaration, at paragraphs 9 to 21, Dr. Broadus, an expert in the field, understands that the teachings of the present application, when considered with the findings of Exhibit B as herein provided, to provide a therapeutic effect with respect to bone formation.

The Examiner has not contested the fact that the present application provides a clear description of the findings of the present invention wherein PTH and PTHrP are determined to be substrates of the type II integral membrane endopeptidase, *PEX*. In accordance with the additional data as herein provided as Exhibit B, it is evidenced that the *PEX* enzyme has the capacity to cleave PTH and PTHrP. Furthermore, the data as herein provided confirms that *PEX* can be inhibited so as to effect an increase in PTHrP protein levels in the osteoblast microenvironment. Exhibit B details *in vivo* data as obtained by the Applicant in support of the use of *PEX* inhibition to effect bone formation *in vivo*. Accordingly, Applicant respectfully submits that the data as herein shown as Exhibit "B" supports the enablement of the claimed subject matter of the present application, namely claims 7-10 whereby the modulation of *PEX* to provide a method for treating metabolic bone disease is evident. Accordingly, Applicant believes that these teachings warrant claims of a scope commensurate with those currently on file in the present application and directed to a novel platform for the treatment of bone disease. Reconsideration of the Examiner's rejections on the basis of a lack of enablement is also herein requested.

The Examiner has also rejected claims 7 and 8 of the present application as indefinite as they do not recite any method steps. Applicant respectfully traverses the Examiner's rejections in this regard in that the objected method claims include the step of

modulating *PEX* expression or activity wherein such modulation results into modulation of PTH and/or PTHrP levels. Accordingly, claim 7 and 8 of the present application embody the use of determining *PEX* activity in a therapeutic context whereby PTH and/or PTHrP levels are modulated *in vivo* to obtain the desired therapeutic effect with respect to bone breakdown and/or bone formation. Favourable reconsideration of the Examiner's objections in this regard is also respectfully requested.

The Examiner has maintained his earlier objections with respect to the novelty of claims 7-10 and 23-28 of the present application in view of the earlier teachings of Vickery et al. or Chorev et al. Applicant once again maintains that the teachings of Vickery et al. are directed to the systemic administration of PTHrP analogs which do not effect an anabolic result in bone nor teach of a method for modulating the levels of PTH or PTHrP in bone as taught in accordance with the present invention. Furthermore, Chorev et al. also teach of the low dose administration of PTH, PTHrP or related compounds for the purpose of promoting bone formation. This prior art reference does not establish the role of *PEX* in the modulation of PTH or PTHrP nor teach of a corresponding endogenous therapeutic effect with respect to bone breakdown and/or bone formation. The Examiner's attention is once again directed to the comments of Dr. Arthur Broadus in the enclosed Declaration (paragraphs 22-24), which further supports the novel distinctions of the present invention thereover.

Applicant advise the Examiner that page 9 of the enclosed Declaration by Dr. Arthur E. Broadus includes a typographical error in the header which indicates that the document is a "DRAFT:WORK IN PROGRESS". Applicant advises that the appearance of this header is the result of an inadvertent typographical error, and that the enclosed Declaration is a final, notorized copy.

Favourable reconsideration of the present application in accordance with this Request for Continued Examination as herein provided, and in view of the comments and evidence as provided, is herein respectfully requested.

In order to facilitate the prosecution of the present application, Applicant would like to arrange to discuss the details of the enclosed response with the Examiner in due

course at a time of the Examiner's convenience. Applicant's agent will follow up in this regard early in the new year.

Respectfully submitted,
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